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REVIEW

Prophylaxis of infective endocarditis in patients with congenital heart disease in the context of recent modified guidelines

Prophylaxie de l'endocardite infectieuse et cardiopathies congénitales dans le contexte des nouvelles recommandations

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Summary Infective endocarditis (IE) is a life-threatening complication that may impair significantly the long-term prognosis of patients with cardiac disease. The profile of IE has changed over recent decades, with a decreasing prevalence of rheumatic fever and increasing survival of patients with congenital heart disease (CHDs). Given the high rates of morbidity and mortality, and based on previous experimental studies, antibiotic prevention of IE has long been recommended for at-risk groups. Serial revised guidelines for prophylaxis have been published over the years. The most recent recommendations differ dramatically from previous guidelines and provide new insights into the prophylaxis of IE. Emphasis is put on oral activities (particularly brushing teeth) as both buccal and skin hygiene may present the greatest threats for individuals at-risk of IE. Significant limitations in both at-risk patients and procedures result in a potential and substantial change in the practice of clinicians and raise concerns about the safety and reliability of these new recommendations for patients with CHD.

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Abbreviations: AHA, American Heart Association; ASD, atrial septal defect; CHD, congenital heart disease; IE, infective endocarditis; MVP, mitral valve prolapse; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

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MOTS CLÉS

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Résumé L'endocardite infectieuse (EI) est une complication grave potentiellement létale susceptible de grever le pronostic à long terme des patients porteurs d'une pathologie cardiaque. Le profil actuel de l'EI d'est modifié depuis les dernières décennies, secondairement à la régression du rhumatisme articulaire aigu, et l'augmentation de la survie des patients porteurs de cardiopathie congénitale. Face au risque important de morbidité et mortalité de l'EI et sur la base d'études expérimentales, la prophylaxie antibiotique de l'EI a été recommandée pendant de nombreuses années pour les groupes à haut risque. Plusieurs révisions des consignes de prophylaxie ont été émises au cours du temps. Les plus récentes diffèrent des précédentes de façon notable et supposent une modification radicale des principes de prévention de l'EI. Ces nouvelles recommandations arguent que les activités de la vie courante concernant l'hygiène buccale et cutanée représentent les situations où le risque d'EI est le plus important pour l'individu. Ainsi la réduction drastique à la fois des groupes et des procédures à risque conduisant à un changement radical de pratique des cliniciens, conduit également à s'interroger sur sa fiabilité et les conditions de sécurité de son application pour les patients porteurs de cardiopathie congénitale.

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Incidence and epidemiology of infective endocarditis

The incidence of infective endocarditis (IE) is reported to vary from 1.5 to six cases per 100,000 persons per year in adults. The percentage of IE in congenital heart diseases (CHDs) has increased relative to the decrease in rheumatic fever [1]. IE is supposed to occur much less frequently in children. However, more complex surgical CHD procedures with implanted material and prostheses and/or residual lesions are likely to result in ongoing IE occurrence. Moreover, more children can currently reach adulthood, even with complex CHD, so the cohort of patients with CHD is increasing. The relative incidence of IE is therefore likely to remain the same or even increase in paediatric and adult patients with CHD. An IE diagnosis and its sequelae are reported to account for 4–5% of in-hospital admissions of patients with CHD and a 2.3% frequency of adult-onset IE in adults with CHD. As a result, IE represents a lifelong risk in these patients. Various factors may impact on the level of risk, such as the type of underlying cardiac disease, the presence of prosthetic material and the microbial causal agent.

Prognosis of infective endocarditis (IE)

Despite improvement in early diagnosis, management, microbial diagnosis and therapeutics and even surgical techniques, the morbidity and mortality rates of IE remain significant [2]; the mortality rate varies from 10–15%. Therefore, IE represents a life-threatening, ongoing complication that may impair long-term outcomes in patients with CHD [3].

Data from the literature have shown IE to be less severe in children, which might be due to the higher proportion of right-sided IE in patients with CHD, particularly in those with a ventricular septal defect (VSD)-located infection [4–7].

In a recent review of IE in CHD, Knirsch et al. reported a 10% overall mortality rate, a 14% surgical mortality rate and a recurrence rate of inferior than 3% [8]. Besides early

mortality and morbidity, IE may also impact on the long-term functional status of patients with CHD, considering that many of them were asymptomatic before the IE occurred [9]. In our own long-term experience with IE in adult and paediatric CHD patients, more than 50% of deaths in this cohort can be directly related to IE, while others are due to either IE sequelae management or CHD outcomes, regardless of the IE episode [2].

Pathogenesis

Three major components must interact to result in IE:

- the underlying cardiac lesion and endocardial damage;
- the circumstances leading to significant lesions of the mucosa, which are susceptible to bacteraemia;
- the volume of the microbial inoculum and virulence of the bacterial agent.

The key factor for IE to develop is firstly endocardial damage. This lesion allows fibrinogen deposits, platelet aggregation and thrombi formation. Interactions with circulating pathogens may promote microbial adherence to thrombi, resulting in the development of an IE-specific lesion (so-called vegetation). A prosthetic surface is particularly exposed to fibrinogen binding and also promotes turbulence of blood flow and endothelial injuries, making prosthetic materials high-risk factors for IE.

Given the prognosis, morbidity and high cost of management of IE, prophylaxis has long been recommended in an attempt to minimize the incidence of IE. Guidelines have been published and revised over the years, to define the underlying CHD level of risk, the procedures and events that carry the highest risk and the protocols for antibiotic prevention of IE, thereby identifying 'who' should benefit from prophylaxis, 'when' to adequately apply prophylaxis and 'how' to administer prophylaxis. Nevertheless, IE still occurs and its incidence is not lessening significantly, which raises the question of whether non-compliance or lack of efficacy (or both) is implicated.

As yet, no randomized study has been conducted to elucidate whether or not IE prophylaxis should be applied, and if it should, then to whom and when it should be applied. Lockhart et al. [10] conducted a prospective, comparative study designed to compare subjects who received amoxicillin before tooth extraction with subjects who had no antibiotics and were given a placebo before the dental procedure. The authors showed that bacteraemia was less frequent in the amoxicillin group (33%) than in the placebo group (84%) but this result does not demonstrate that IE would have occurred. Recommendations were based on experimental animal studies that previously demonstrated the efficacy of antibiotics in preventing IE when administered before bacteria inoculation [11], and also on medical practice and experience [12]. Conversely, most published data have reported that IE can still occur despite prophylaxis being applied according to current recommendations.

Thus, recommendations for IE prophylaxis have eased dramatically over the years. Based on case-control studies, expert opinion and daily practice, the last revised American Heart Association (AHA) guidelines published in 2007 resulted in a drastic reduction and limitation of the cardiac diseases and procedures in which IE prophylaxis is indicated [13].

Rationale for revised recommendations for infective endocarditis (IE) prophylaxis

Several main points have led to the new expert consensus in the field of IE prophylaxis.

First, 'IE is much more likely to result from frequent exposure to random bacteraemia associated with daily activities than from bacteraemia caused by a dental, gastrointestinal tract or genitourinary tract procedure'. IE occurs rarely and is unlikely to impair significantly the overall prognosis of patients. The ratio of the number of treated IE cases to the number of cases undergoing prophylaxis is far too low to support routine prevention of IE. 'Prophylaxis may prevent an exceedingly small number of cases of IE, if any, in individuals who undergo a dental, gastrointestinal tract or genitourinary tract procedure'. However no mention exists about the costs due to IE management (hospitalization, antibiotics, techniques for anatomical and microbial diagnosis, iterative surgeries, long-term follow-up, management and complications) or about patients' vital and functional prognosis. The low cost of prophylaxis has to be weighted against the high costs of IE diagnosis and treatment.

The second and most important point is that procedures are less likely to cause IE than daily activities and poor patient hygiene. Que and Moreillon [14] assessed the theoretical cumulative bacteraemia resulting from daily oral activities such as brushing teeth or chewing and concluded that 1-year everyday bacteraemia is six million times greater than that associated with 1-year bacteraemia due to a dental extraction. Thus, it is not clear whether daily-activity related bacteraemia could reach the cut-off inoculum volume to seed the cardiac tissue [15]. Therefore, the experts stated that 'Maintenance of optimal oral health and hygiene may reduce the incidence of bacteraemia from daily

activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE'.

Another point is that some patients who undergo dental procedures have an underlying cardiac disease that has not been recognized. We observed such cases in our experience of IE in CHD, where the underlying diseases were mostly minor valvular lesions, such as aortic bicuspidia or mitral valve prolapse (MVP). These patients with unrecognized CHD accounted for about 15% of our cases.

Lastly, the experts considered antibiotic side effects, including microbial-induced resistance and anaphylaxis. However, no report has been published about resistance due to one-dose amoxicillin and no case has been reported of death due to antibiotic-induced anaphylaxis, whereas mortality due to IE is still significant and widely reported.

Finally, the revised recommendations were also based on the lack of a controlled randomized study to prove the efficacy of IE prophylaxis. The number of patients necessary to conduct a controlled, randomized trial to assess the effectiveness of IE prophylaxis has been estimated to be superior to 6000 patients per group, which has discouraged centres from initiating such a study [12,16].

Underlying congenital heart disease (CHD)

In previous recommendations, CHDs were classified into high-risk, moderate-risk or mild-risk groups. Recent guidelines resulted in a drastic reduction in the target CHDs for IE prophylaxis and suppression of the CHD classification into at high, moderate or mild-risk for IE, assuming that only patients in the previously-named 'high-risk' group should receive IE prophylaxis. The other CHDs, previously in the moderate-risk or mild-risk groups, are no longer targets for IE prophylaxis [13,17,18].

In summary, cardiac conditions associated with the highest risk of adverse outcome from endocarditis, for which prophylaxis with dental procedures is reasonable, include [13]:

- prosthetic cardiac valve or prosthetic material used for cardiac valve repair;
- previous IE;
- unrepaired cyanotic CHD, including palliative shunts and conduits;
- completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure. In this case, prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure;
- repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization);
- cardiac transplantation recipients who develop cardiac valvulopathy.

Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

It is well recognized that surgical repair may nullify the lifetime risk of IE, provided that neither residual lesion nor prosthetic material is present. In fact, only a few CHDs can

be completely cured; some kind of residual lesion often persists (residual shunt, valve anomaly, etc.) or prosthetic materials are implanted (valvular prosthesis, tubes, anastomosis, patches).

Considering that high-velocity and turbulent flow are more likely to generate endothelial lesions and promote IE, risk varies consecutively according to the underlying cardiac lesions, although the guidelines no longer attach any importance to this assessment.

Lastly, some IE episodes were reported in patients who underwent interventional procedures, which raised the question of whether these cases should receive prophylaxis.

Regarding cyanotic unrepaired or palliated CHD, there is a common consensus for IE prevention, as well for patients who have experienced a previous IE episode. These CHDs are considered at highest risk for IE.

IE prevention is no longer recommended in repaired CHD, in case of no residual lesion [13] but prophylaxis should be applied within the first 6 months after repair, while endothelialization develops, particularly after patch closure of a VSD. However, any residual shunt or associated lesion, such as aortic insufficiency, will justify lifelong IE prophylaxis, given that endothelialization cannot occur. This assessment seems to be in discrepancy with the same native unrepaired lesion (i.e. VSD or aortic regurgitation).

A review by Knirsch et al. aimed to estimate the mean frequency of repaired and unrepaired CHD in an IE series [8]. The author showed that IE is a lifetime risk for repaired, non-operated and palliated CHD. Aortic and mitral valves are the most frequent targets for IE, including unoperated and non-haemodynamically significant valvulopathies. If unrepaired, VSD is the most frequent CHD associated with IE. The cumulative incidence of IE over a 25-year follow-up after surgical repair (or interventional procedure) is as follows, according to the CHD:

- 1.3% for tetralogy of Fallot;
- 2.7% for VSD;
- 2.8% for primum-type atrial septal defect (ASD);
- 3.5% for coarctation of aorta;
- 13% for aortic valve stenosis;
- 0% for ostium secundum ASD, patent ductus arteriosus (PDA) and pulmonary valve stenosis.

A 30-year follow-up demonstrated a cumulative IE incidence of 4.0% for transposition of the great arteries, 5.3% for pulmonary atresia with intact ventricular septum and up to 6.4% for VSD [19]. Risk is evidently increased by any prosthetic material and devices.

Procedures

Endocardial lesion is the primary target for microbial adherence. Therefore, any cause of significant bacteraemia will potentially be the initial factor in the occurrence of IE. In 1909, Horder [20] observed a link between mouth infection and IE. Tooth extraction was later shown to induce bacteraemia. Moreover, the microbial agents most susceptible to causing IE belong to the *Streptococcus* group from oral origin. Indeed, any procedure that could potentially cause bacteraemia was thought to represent a potential route of entry. Dental procedure was the leading target for antibiotic

prophylaxis; animal experiments demonstrated the effectiveness of antibiotics in preventing the development of IE after experimental inoculation of bacteria [11]. Based on these experimental studies and on common practice in patients who were diagnosed with IE within several weeks after an unprotected dental procedure, protocols for prevention of IE have long been applied to minimize risk and prevent bacteraemia and subsequent development of IE.

IE can occur despite an adequate current protocol for IE prevention having been applied but most of the time-detailed data about antibiotic administration are lacking. Imperiale et al. showed that only 13% of patients who experienced IE after an unprotected dental procedure had received prophylaxis compared with 63% of matched controls who had no IE [21].

Conversely, not only dental procedures, but also any other procedure susceptible to damaging the mucosa was supposed to carry the same risk. In particular, digestive, urinary or bronchial procedures were also involved in previous recommendations for IE prophylaxis.

On the basis of a *Cochrane* review that showed little evidence to support the published guidelines [22], revisited guidelines have completely changed the previous assessments. Indeed, no randomized, controlled trial exists to demonstrate the efficacy, reliability or safety of antibiotics for the prevention of IE. Such a study is still questionable because of ethical issues and the prohibitively high number of enrolled patients required per group.

It is known that bacteraemia is more likely to result from daily activities such as chewing, brushing teeth and using water irrigation devices for tooth cleaning than from dental procedures [15]. Experts have identified oral hygiene as the most important endpoint for bacterial prevention of IE.

Clinical reports and series often fail to prove the link between IE and a previous procedure. The causative event can only be retrieved in one third of cases. Even in case of close temporal association between a precedent event or procedure and onset of IE, it is still hardly possible to determine whether the bacteraemia was induced by the procedure or by other daily activities or poor oral hygiene [12].

The new guidelines recommend prophylaxis for any procedure that may alter the gingival tissue, the periapical region or induce perforation of oral mucosa (i.e. biopsies, suture removal, placement of orthodontic bands, tooth extractions and periodontal procedures). Conversely, the following procedures and events do not need prophylaxis: routine local anaesthetic injections through non-infected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa [13].

Prophylaxis is no longer recommended for any other non-dental procedures. Therefore, digestive endoscopic manipulations or procedures in the respiratory tract do not require antibiotic administration, even in groups at high-risk, unless ongoing tissue infection is recognized. This assessment also includes skin tissue; the AHA guidelines provide advice against body piercing but give no clear recommendation. For patients with the highest risk of IE who undergo a procedure that involves infected skin or

musculoskeletal tissue, the therapeutic regimen administered for treatment of the infection should contain an agent active against *Staphylococcus* and beta-haemolytic *Streptococcus* [23].

Guidelines currently focus on daily mouth and skin hygiene. In a double-blind, placebo-controlled study, Lockhart et al. assessed bacteraemia in 290 subjects randomized to tooth brushing or single tooth extraction with amoxicillin prophylaxis or single tooth extraction with identical placebo [24]. The cumulative incidences of endocarditis-related bacteria from blood draws were 23, 33 and 60% for the tooth brushing, extraction-amoxicillin and extraction-placebo groups, respectively ($P < 0.0001$). Culture positivity was lower in patients receiving amoxicillin. The authors concluded that the 23% positive cultures after tooth brushing and the high frequency of oral hygiene activities might make tooth brushing the highest at-risk circumstance for IE.

Unanswered questions and concerns

Owing to lack of evidence, all the recent recommendations are class IIa and level of evidence B or C. Given that no randomized, controlled study is currently available, the level of evidence for these new recommendations is not stronger than before.

Underlying congenital heart disease (CHD)

Native, unrepaired CHDs, such as left-to-right high-velocity shunts or mild mitral and/or aortic valvulopathies, are no longer targets for IE prophylaxis. Nevertheless, IE can occur in patients with such underlying CHD, as widely reported in the literature. Knirsch and Nadal reviewed the clinical entity of CHD associated IE between 1960 and 2007, considering reports of more than 25 IE cases, and provided information on the cardiac diagnoses and procedures performed.

VSD is the most frequent unrepaired CHD associated with IE [25]. It accounted for 30% of cases in our experience of IE in CHD [2]. Most of these cases were small, haemodynamically non-significant VSD and/or associated with aortic regurgitation. The incidence of IE in unrepaired VSD is 1.5–2.4 per 1000 patient-years. The natural history of VSD shows that the estimated lifetime risk for IE is 9.7% at age 30 years and 12% by the end of life [26].

Bicuspidia of the aortic valve has long been considered an at-risk CHD. The prevalence of this anomaly is 0.5–2%. Aortic valve bicuspidia may complicate over time with aortic stenosis and mostly aortic insufficiency. Recent estimates of IE in aortic bicuspidia are around 0.3–2% per year [27].

Isolated PDA frequency is about 1 in 2000 full-term infants. Most patients are asymptomatic and the left-to-right shunt is usually non-significant [28]. However, common practice has long recommended closure of PDA because of a lifetime risk of IE. Percutaneous closure of PDA has become the leading therapeutic option for infants and children with haemodynamically non-significant PDA.

Patients with MVP have a threefold to eightfold higher risk of developing IE, with an estimated incidence of about 0.02% per year, but only in those with an additional mitral regurgitation [29]. Endocarditis occurs in MVP at a rate of 0.1 cases per 100 patient-years [30].

With the improved resolution and sensitivity of newer generations of echocardiograms, clinicians often face the dilemma of the patient with MVP and 'trivial' or 'minimal' mitral regurgitation, making the decision to apply prevention of IE a matter of debate. Recent criteria from the AHA guidelines may help with this decision, as valve prolapse of 2 mm or more above the mitral annulus is required for diagnosis [31]. This change has effectively lowered the prevalence of MVP from 4–8% of the general population to 2–3%.

The recent guidelines for prevention of IE published by the AHA in 2007 [13] no longer consider native unrepaired cardiac lesions to be at-risk of IE. In particular, prophylaxis is no longer recommended in patients with MVP, bicuspidia, PDA or VSD. Nevertheless, IE can occur in these patients and is reported in all published series. This discrepancy probably contributes to clinicians being concerned about whether to follow these guidelines fully or not; some would continue prevention in patients they feel to be at significant risk.

Procedures

Streptococcus and *Staphylococcus* are the two main microbial agents responsible for IE in CHD, coming from either the oral cavity or the skin. Daily buccal activities are considered as the current leading causes of bacteraemia. However, this concept of cumulative bacteraemia has not been currently supported by an experimental study showing the magnitude that everyday bacteraemia can reach and whether it exceeds the theoretical bacterial inoculum volume cut-off needed to induce IE. It is also unclear if repeat everyday bacteraemia would promptly clear from the body or would induce a cumulative level of circulating microbial agents. Moreover, no mention is provided about the bacterial virulence that would lessen the threshold of at-risk bacteraemia or about the immunosuppressive status of the patient.

It is commonly recognized that the skin may be widely colonized by commensal but also pathogenic *Staphylococcus* agents [32]. Any cutaneous damage, including tattooing or body piercing, may therefore induce bacteraemia, even in the absence of proven tissue infection. The level of cutaneous risk might be underestimated by the new guidelines, regarding the frequency of *Staphylococcus* IE.

Clinicians' behaviour

Faced with these new recommendations, Pharis et al. assessed the impact of the 2007 AHA IE prophylaxis guidelines on clinician practice in a multicentre, cross-sectional, web-based survey sent to Canadian, Australian, New Zealand and American paediatric and adult CHD cardiologists in 2008 [33]. The response rate was 55%. Cardiologists were divided between recommending versus not recommending prophylaxis for perimembranous VSD status after surgical patch closure with no residual shunt, 3 months postoperatively.

The greatest proportion of circumstances in which cardiologists discontinued prophylaxis were 'small muscular VSD, no previous endocarditis' and 'small audible patent ductus arteriosus'. Twenty-eight percent of the clinicians felt that the new guidelines left some patients at-risk. Therefore,

although the 2007 guidelines have resulted in changes in IE prophylaxis, wide heterogeneity has been observed among the cardiologists who are in charge of these patients. These results show that many of them feel concerned about the safety of these recommendations, given the severity and life-threatening risk of IE.

As claimed by Weaver et al., 'lack of evidence is not necessarily equivalent to lack of benefit' and 'if prophylaxis is futile, why select high-risk patients for prophylaxis?' [34].

Protocols for antibiotic prophylaxis

According to the current recommended protocols for antibiotic prophylaxis, an oral, single dose of antibiotic should be administered 30–60 minutes before the invasive procedure, only in patients in the high-risk group and for dental at-risk procedures. If the dose cannot be given before, it should be done within 2 hours following the procedure [32]. First-line antibiotics are focused on *Streptococcus* infection and amoxicillin is the recommended first-option therapy. In case of allergy, a macrolide should be chosen. For specific, skin-related procedures, the regimen should mostly focus against the *Staphylococcus aureus* microbial agent. Severe anaphylactic events have not been reported, nor have single doses of antibiotics induced resistance.

These are the current published recommendations for antibiotic prophylaxis:

- if the patient is able to take oral medications, amoxicillin is the first-line antibiotic and should be administered at a single dose of 50 mg/kg in children (30–60 minutes before procedure) or 2 g in adults;
- if the patient is unable to take oral medications, intravenously or intramuscular administration of antibiotic is required, with either ampicillin (50 mg/kg in children, 2 g in adults) or cefazolin (or ceftriaxone) (50 mg/kg in children, 1 g in adults);
- if the patient is allergic to penicillin or ampicillin and able to take oral medications, penicillin is replaced by either cephalexin (50 mg/kg in children, 2 g in adults) or clindamycin (20 mg/kg in children, 600 mg in adults) or azithromycin or clarithromycin (15 mg/kg in children, 500 mg in adults);
- the patient is allergic to penicillin or ampicillin, but unable to take oral medications, intravenously or intramuscular administration of antibiotic is required, with either cefazolin or ceftriaxone (50 mg/kg in children, 1 g in adults) or clindamycin (20 mg/kg in children, 600 mg in adults).

Conclusion

The incidence and severity of IE has not decreased significantly over the years. CHDs are specifically exposed to IE risk. According to recent revised guidelines, some unrepaired native congenital heart defects are no longer targets for IE prophylaxis. Recommendations emphasize daily oral activities and poor buccal and skin hygiene as the leading causes of IE. These substantial changes in IE prophylaxis for paediatric and adult CHD patients raise unanswered questions for cardiologists about who should and when to apply

prophylaxis. Further studies are required to elucidate and assess the consequences and impact of the new guidelines on CHD patient outcomes.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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